

# Evidence of a Causal Role of Winter Virus Infection during Infancy in Early Childhood Asthma

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**Rationale:** Bronchiolitis during infancy is associated with an increased risk of childhood asthma. Whether winter viral infections cause asthma or are a manifestation of a predisposition to asthma development is unknown.

**Objectives:** To study the relationship of winter virus infection during infancy and the development of childhood asthma.

**Methods:** We studied over 95,000 infants born between 1995 and 2000 and followed through 2005 who were enrolled in the Tennessee Medicaid program from birth through early childhood to determine whether infant birth in relationship to the winter virus peak alters the risk of developing early childhood asthma.

**Measurements and Main Results:** Among 95,310 children studied during five winter virus seasons from birth through early childhood, the risk of developing asthma tracked with the timing of infant birth in relationship to the winter virus peak. Infant birth approximately 4 months before the winter virus peak carried the highest risk, with a 29% increase in odds of developing asthma compared with birth 12 months before the peak (adjusted odds ratio, 1.29; 95% confidence interval, 1.19–1.40). Infant age at the winter virus peak was comparable to or greater than other known risk factors for asthma.

**Conclusions:** Timing of birth in relationship to winter virus season confers a differential and definable risk of developing early childhood asthma, establishing winter virus seasonality as a causal factor in asthma development. Delay of exposure or prevention of winter viral infection during early infancy could prevent asthma.

**Keywords:** asthma; respiratory winter virus infection; timing of birth

Worldwide, the prevalence of asthma rose 100% from 1985 to 2001. About 300 million people have asthma, 255,000 die from it, and deaths could increase by 20% in the next 10 years (1). The problem is severe worldwide, and developing countries are particularly burdened (2). Efforts to find effective and targeted primary and secondary asthma prevention measures are needed.

One potentially modifiable environmental factor associated with asthma development is infant respiratory viral infections. However, whether infant bronchiolitis causes asthma or serves as a marker for those genetically predisposed to develop disease is unknown. This is an important question to address, however, as if it is causal, prevention is possible. Because it is not ethical to randomize infants to early viral exposure or not and because a population-based incidence study would be labor consuming

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## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Bronchiolitis during infancy is associated with an increased risk of childhood asthma. Whether common respiratory viruses, which infect all infants, cause asthma or whether infection is a marker of those predisposed to developing asthma is unknown.

### What This Study Adds to the Field

Timing of birth in relationship to the annual winter virus peak predicts an infant's likelihood of developing childhood asthma. This study provides strong evidence for a causal relationship of winter viruses with early childhood asthma.

and costly, observational study designs are needed that can answer the question of whether bronchiolitis causes asthma or is a marker of a child with asthma.

The relationship between viral infections and asthma is important from two perspectives. First, it is well established that among infants who require hospitalization for viral bronchiolitis, up to 43% develop asthma by 13 years of age, whereas the estimated prevalence in the U.S. population is approximately 8 to 10% (3–8). Second, viral infections are the most frequent and important cause of asthma exacerbations in children, implicated in up to 85% of disease exacerbations (9–11). Respiratory viral infections during infancy may have an acute and long-term impact on lung and immune system development, resulting in an increased risk for childhood asthma (10, 12–20).

The risk of respiratory syncytial virus (RSV) bronchiolitis is associated with seasonality of birth (21, 22). If similar birth timing determines asthma risk, this would suggest that bronchiolitis or some factor closely associated with bronchiolitis causes asthma. We hypothesized that infant age at the winter virus peak would confer a differential and definable risk of developing early childhood asthma. To test this hypothesis, we conducted an investigation of over 95,000 children born between 1995 and 2000 and followed until early childhood through 2005. Some of the results of these studies have been previously reported in the form of abstracts (23, 24).

## MATERIALS AND METHODS

### Subjects

We conducted a population-based birth cohort study of 95,310 children who were born in Tennessee from 1995 to 2000 and continuously enrolled in Tennessee Medicaid (TennCare) until 5.5 years of age through 2005, representing 25% of the annual births in Tennessee. Asthma was defined in two ways. First, early childhood asthma was